REMARKS

I. The Invention

The subject matter of the present invention is an insoluble elastic matrix graft derived from ureter or urethra smooth muscle tissue. The present inventors established a novel method for preserving the naturally occurring acellular collagen/elastin framework in the ureter or urethra smooth muscles. The most surprising feature of the matrix is that, unlike matrices made by following the teaching of prior art, this collagen/elastin matrix retains the natural structural integrity and is therefore impermeable to urine, even when under pressure. Further, the acellular matrix is low in antigenicity, allows re-cellularization, and performs remarkably in restoring the functions of ureter or urethra. This is documented by several references previously made of record and further demonstrated by Dr. Tanagho in his declaration.

II. Status of the Claims

Claims 1-23 were originally filed and later canceled. Claims 24-28 have been added and are currently pending under examination.

III. Claim Rejections

A. Double Patenting

Claims 24-28 remained rejected under the judicially created doctrine of obviousness-type of double patenting as allegedly being unpatentable over claims 1, 3, 4, 8, and 10 of U.S. Patent No. 6,371,992. Applicants are willing to consider filing a terminal disclaimer once all pending claims are found otherwise allowable.

B. 35 U.S.C. §103

In the Office Action of June 17, 2005, the Examiner maintained the rejection of claims 24-28 under 35 U.S.C. §103(a) for alleged obviousness over Gregory (U.S. Patent No. 5,990,379) in light of Bishopric *et al.* (U.S. Patent No. 5,855,620) or Goldstein (U.S. Patent No. 5,632,778) or Abraham *et al.* (U.S. Patent No. 5,993,844). Applicants respectfully traverse the rejection, particularly in light of the Rule 132 declaration by Dr. Tanagho.

1. Antedating Abraham et al.

In the Office Action mailed June 17, 2005, the Examiner again declined to accept Applicants' Rule 131 declaration and the Probst reference as evidence for the purpose of antedating Abraham *et al.* The Examiner first argued that according to MPEP §716.10 (citing *In re Costello*), a reference that is once the subject matter of a Katz declaration cannot be used to antedate another reference. In the response filed May 3, 2005, Applicants pointed out the significant factual differences between *Costello* and the present case, and argued that these factual differences would render it inappropriate to apply the broad reading of *Costello*. Yet the Examiner did not address this point in the June 17, 2005, Office Action.

As the second reason for his decision to hold the 131 declaration inadequate, the Examiner stated that the claimed invention is not disclosed by the Probst paper, because the claimed invention of this application relates to the species of ureter or urethra, whereas the Probst paper relates to the species of bladder. In the response filed May 3, 2005, Applicants pointed out that, according to MPEP §715.02 and §715.03, a prior invention need not show the completion of the invention involving the same species; so long as the species completed prior to the reference date establishes an adequate generic applicability, a 131 declaration can be sufficient. Since the Examiner has taken the position, in raising the double patenting rejection, that the species of bladder, ureter, and urethra are all obvious over each other for the purpose of preparing an acellular matrix graft, one following the same reasoning would then necessarily arrive at the conclusion that the successful preparation of a matrix graft using the species of bladder (as shown in the Probst reference) can adequately support a generic invention that also encompasses the species of ureter and urethra. The 131 declaration with the Probst reference should then suffice to antedate the Abraham reference following this logic. Again, the Examiner did not address this specific point in the June 17, 2005, Office Action.

Instead, the Examiner reiterated his earlier arguments in the previous Office Action, and further asserted that, in the first full paragraph on page 5 of the June 17, 2005, Office Action, "Applicants argued that the claimed invention and that of Probst are similar enough to be obvious, yet Applicants also argue that the primary references, of the Section 103 rejection, are

not similar enough to be obvious. This appears to be inconsistent." The Examiner's statement has incorrectly characterized Applicants' position.

First, ***it is the Examiner's position***, by raising the double patenting rejection, that the invention of the instant application is obvious over the invention of its parent application, which is disclosed in the Probst reference. In contrast, Applicants have only stated that ***if one is to follow the Examiner's reasoning***, then he will find the disclosure in the Probst paper sufficient to support a generic invention that encompasses all three species of bladder, ureter, and urethra. Indeed, Applicants are yet to submit a terminal disclaimer disclaiming the term over that of the patent issued from the parent application.

Secondly, even if Applicants have accepted the Examiner's position, there still will not be any necessary inconsistency for Applicants to further take the position that the claimed invention of this application is non-obvious over the references cited for §103 rejection. In the parent case, the same references were cited for a §103 rejection, which was withdrawn by the same Examiner prior to the issuance of the parent patent. In other words, the Examiner considers the invention of the parent application, which is described in the Probst reference, not obvious over the §103 references. Applicants agree with the Examiner on this point. Logically, if the present invention is not patentably distinct from that of the parent application, which has been found to be non-obvious over the §103 references, then the present invention is not obvious over the same references either. It is therefore clear that Applicants have not taken any inconsistent positions during prosecution of this application and its parent application.

In Applicants' last response (filed May 3, 2005), Applicants have fully addressed each and all of the reasons the Examiner provided as the basis for rejecting the 131 declaration to antedate the Abraham reference. The Examiner has made no direct response, however, in the latest Office Action, to these specific points brought up by Applicants. In this paper, Applicants have further addressed the Examiner's concerns that were raised in the latest Office Action. In view of all the discussions made of record, Applicants respectfully request that the Examiner reconsider the Rule 131 declaration and accompanying evidence for antedating the Abraham *et al.* reference.

2. Gregory in Light of Bishopic et al. or Goldstein et al. or Abraham et al.

Even if Abraham *et al.* is still considered a prior art reference against the pending claims, Applicants further contend that no *prima facie* obviousness has been established.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143. By way of a Rule 131 declaration by Dr. Tanagho, a named inventor on this application, Applicants establish that: first, the cited references does not necessarily motivate or suggest to one of skill in the art to combine the teaching of these references; and second, there is no reasonable expectation of success to arrive at the present invention by combining the teaching of the cited references.

i. No Motivation to Combine

First, Dr. Tanagho establishes why there is no motivation to combine the teaching of the primary references (Bishopric, Goldstein, and Abraham) and the secondary reference (Gregory): the primary references relate to an acellular collagenous matrix, whereas the secondary reference relates to elastin extraction and purification. Because of the distinct results achieved by the processes, one of skill in the art would not be motivated to combine these references. See paragraph 6 of the declaration.

The pending claims of this application are directed to a collagen/elastin matrix derived from ureter or urethra smooth muscles, thus, in paragraphs 7-9 of the declaration, Dr. Tanagho provides an introduction of the important distinctions between the properties of elastin and collagen, as well as the methods for their extraction or preservation. According to Dr. Tanagho, under a light microscope, collagen and elastin form a matrix of interwoven fibers. Under an electron microscope, both collagen and elastin individually form their own fibrous matrix. These two proteins have distinct characteristics and thus contribute to different aspects of the collagen/elastin matrix: collagen imparts strength and elastin imparts flexibility. Collagen,

a fibrous protein consisting of a combination of types I, II, III, *etc.*, is readily solubilized by conditions that do not appreciably solubilize elastin. When present within a matrix, collagen derives its strength to a large extent from the length of the fibers. Furuto *et al.* (made of record with Applicants' response of May 3, 2005, as Exhibit 2) describe a preferred method of solubilizing collagens, where selective extraction of collagen involves using salt and diluted acid (*see, e.g.*, pages 43-44).

On the other hand, elastin and its purification procedures are described in the review articles by Rosenbloom (made of record with Applicants' response of May 3, 2005, as Exhibit 3) and Soskel *et al.* (made of record with Applicants' response of May 3, 2005, as Exhibit 4). According to Rosenbloom, the fibers of elastin are called elastic fibers, which are 90% elastin and 10% microfibrillar components. Soskel *et al.* also describe elastin as a "heavily cross-liked meshwork, perhaps best described as a fiber rather than as a protein. It is an infinitely large polymer" (*see, e.g.*, page 196). The flexibility of elastin is due to its extensive crosslinking between polypeptide strands.

In the present application, the claimed matrix is a collage/elastin matrix that maintains its native strength and flexibility. This means that the fiber lengths and cross-linking have not been chemically altered to weaken the integrity of the matrix. The matrix is also intact in that it can retain urine and does not have rips or tears through which urine can pass.

Regarding the references cited by the Examiner, Dr. Tanagho points out in paragraph 10 of the declaration that, among the three primary references (Bishopric, Goldstein, and Abraham) cited to form the basis of the obviousness rejection, the Bishopric reference describes a generic method for producing a collagen/elastin matrix from tissues, where the descriptions generally relate to body tissues, with focus on vascular tissues such as heart valves. This is the most apparent in the examples of this reference. Similarly, the Goldstein reference describes bioprothesis derived from tissues following a decellularizing process involving enzymatic treatment. The specific tissue types discussed in this reference are skin and heart valves, although the author does not limit his invention to these tissue types. The Abraham reference teaches the production of an acellular collagenous matrix using a chemical method.

Again, Abraham *et al.* refer to the tissue types either in a general sense or naming specific types that do not include ureter or urethra.

Dr. Tanagho further discusses the secondary reference by Gregory in paragraph 11 of the declaration: the Examiner apparently took the position that this missing limitation, *i.e.*, deriving a collagen/elastin matrix from ureter or urethra smooth muscle tissue, can be found in the Gregory reference. The Gregory reference teaches methods for elastin extraction and purification from various sources, including ureter. This reference, however, describes its matrix as an "elastin matrix" rather than an "collagen/elastin matrix." Elastin is *per se* a "matrix." There is no indication that the methods disclosed by Gregory are preserving the natural collagen/elastin matrix present in tissues such as in the ureter or urethra smooth muscles. For instance, the extraction conditions described by Gregory (column 5, lines 36-55) makes no allowance for preserving the collagen or microfibrillary components. Gregory describes the conventional methods for elastin extraction/purification, which call for acid and base treatment and/or use of heat. Under these conditions, collagen fibers will be severely damaged, if not completely solubilized. In fact, it is explicitly stated in EXAMPLE 3 (column 11, lines 46-58) that the elastin-based biomaterials produced according to the method taught therein "appear translucent, pearly white in color and collapsed when removed from water ***indicating the absence of collagen*** and other structurally supportive proteins" (emphasis added).

Thus, Dr. Tanagho concludes that because of the difference in purpose and in result of the methods taught by Bishopric, Goldstein, or Abraham and by Gregory, a person of ordinary skill in the art would not find any suggestion or motivation from these references to combine the limitations found in these references. Gregory teaches extraction of elastin in a process far too harsh to preserve the intact collagen/elastin scaffolding. An artisan who sets out to prepare a bioprothesis described by Bishopric, Goldstein, or Abraham would find no reason, either in the references or elsewhere, to combine the disclosure of Gregory, as the latter teaches the disruption of the collagenous network and would therefore defeat the purpose of preparing a implantable material having required structural integrity. See paragraph 12 of the declaration.

ii. No Reasonable Expectation of Success

Second, Dr. Tanagho establishes by his declaration that there would be no reasonable expectation of success even if an artisan were somehow inspired to combine the teaching of Bishopric, Goldstein, or Abraham with the teaching of Gregory, and attempted to produce a collagen/elastin matrix derived from tissues other than those actually experimented by Bishopric, Goldstein, and Abraham, there would be no reasonable expectation of success in obtaining such a matrix with the properties as defined in the present application. Dr. Tanagho indicates that this is because there exists significant difference in properties between ureter/urethra smooth muscle and other tissue types used in the methods described by Bishopric, Goldstein, or Abraham. See paragraph 13 of the declaration.

According to Dr. Tanagho, as far as the applicability of the disclosed methods is concerned, Bishopric, Goldstein, and Abraham appear to encompass a whole universe of tissue types. Yet, besides the certain tissue types that have been shown in the examples, these three references do not adequately address the feasibility of their methods in other tissues, particularly those with special properties due to their distinct structure and functionality (*e.g.*, the properties of flexibility and water impermeability of the ureter and urethra) and the ability to serve as an organ-specific scaffold for a recipient's re-growth of the same organ's cellular content and muscular tissue. There is a large number of different types of tissues present in a human body, and the tissues differ drastically in terms of strength, elasticity, and porosity of the cellular matrix. For instance, heart valves are a type of highly specialized tissue in that the tissue is nearly acellular except for a thin external layer of cells that can be readily removed by a variety of treatment methods to achieve a thick, dense, and relatively stiff matrix. In contrast, the intact matrix of smooth muscles such as that forms ureter or urethra provides a waterproof sheath with much higher flexibility. The matrix taught by Bishopric, Goldstein, or Abraham cannot substitute the matrix provided by the present disclosure, because the matrix of the present invention provides some important features that cannot be predicted or expected from the teaching of the cited references: first, the matrix of the present invention must be strong enough retain fluids without leakage, even when under pressure; second, the matrix must be flexible

enough to accommodate changing fluid pressure; third, the matrix can be sutured without compromising its internal integrity or tearing when under pressure; and fourth, the matrix must be able to sustain growth of multiple cell types (muscle, epithelial, mucosal, and nerve) necessary to restore function to the repaired organ. See paragraph 14 of the declaration.

iii. Unexpected Properties of the Claimed Collagen/Elastin Matrix

More importantly, Dr. Tanagho's declaration rebuts *prima facie* obviousness by further demonstrating that the acellular matrix graft of the present invention has surprising and extraordinary properties that are not expected from combined reading of the cited references.

In paragraph 16 of his declaration, Dr. Tanagho attests that the collagen/elastin matrix of the present invention has been shown, in actual testing and use, to possess extraordinary properties that cannot be gleaned from the cited references. Dr. Tanagho points out that the inventors of this application have successfully accomplished the goal of making a matrix that has preserved the native collagen/elastin scaffolding and thus maintained the desired strength and flexibility. This matrix has no antigenicity and readily permits cell repopulation into the collagen/elasting framework. These properties of the matrix as a tissue graft have been tested in numerous studies and the graft has consistently performed well. This is evidenced by Sievert *et al.* (made of record with Applicants' response of May 3, 2005, as Exhibit 5). Three additional publications by the present inventors provide further details in the surprisingly outstanding quality of the ureter/urethra-derived collagen/elastin matrix that allowed successful graft and long term use. The performance of the matrix is particularly remarkable in terms of recellularization and pressure profile (Dahms *et al.*, *Urology* **50**:818-825, 1997; Sievert *et al., J. Urol.* **163**:1958-1965, 2000; and Sievert *et al., J. Urol.* **165**:2096-2012, 2001, made of record with Applicants' response of May 3, 2005, as Exhibits 6-8, respectively).

In paragraph 17 of his declaration, Dr. Tanagho introduces dramatic evidence (slides 1-11) to show that recent effort by the present inventors using the claimed matrix graft for repairing urethra in human patients has proven highly successful. In particular, the claimed invention was used by the inventor on a human subject to correct damaged urethral tissue. More recently, others have referred to the inventor's procedure and copied successfully on patients

around the world. The attached eleven (11) slides (Exhibit B) describe some aspects of the procedure. Slide 1 shows the stenosed (damaged or strictured) urethral tissue that was replaced. Slide 2 shows an x-ray of the stenosed (damaged or strictured) segment of the urethra. Slide 3 shows a chart and numbers of the patient's urine flow before the operation. Slide 4 shows a sketch of the operation. Slide 5 shows the patient's pre-operation condition. Slide 6 shows the donor's (cadaveric) urethral tissue to be grafted into the patient, which donor's tissue was treated using the same process described in this patent application. Slide 7 shows the patient's urethral tissue to be removed. Slide 8 shows the cadaveric tissue of the appropriate size that was treated using the process described in this patent application to be grafted into the patient. Slide 9 shows the sutured donor's tissue implanted into the recipient. Slide 10 shows an x-ray of the grafted urethral tissue of the healthy recipient after the operation. Slide 11 shows a chart and numbers of the healthy recipient's normal urine flow after the operation. This surgical procedure typically involves exposing the stenosed urethral segment and splitting it open ventrally. The cadaveric decellularized urethra is also split open and the appropriate length and width is prepared to be used as an onlay graft over the stenosed urethral segment using 50 absorbable sutures and all the wounds are then closed in the usual manner.

In contrast to the proven success achieved by the matrix graft of this invention, Dr. Tanagho states, a matrix produced from any randomly selected tissue type, including those that have been used by Bishopric, Goldstein, and Abraham, simply cannot be expected to possess the exceptional properties of the matrix graft of the present invention, which are essential for the successful repair of ureter or urethra. The combined teaching by Bishopric, Goldstein, and Abraham and the teaching by Gregory, does not show or suggest use of the decellularized tissue as an organ-specific scaffold for re-growth of specific organs' cellular contents and muscular tissues. See paragraph 18 of the declaration.

Summary

Because the cited references together provide no suggestion or motivation to combine the claim limitations that might be found in the references, and there is certainly no reasonable expectation that such combination would produce a collagen/elastin matrix having the

properties of flexibility, water impermeability, and susceptibility for cell repopulation, which is essential for a graft used for repairing ureter or urethra. Applicants submit that no *prima facie* case of obviousness is established.

Furthermore, the claimed collagen/elastin matrix has been shown to have performed remarkably well in numerous tests, particularly in terms of maintaining structural integrity of the graft, the ability to respond to pressure, and the capability to promote cell re-growth. These characteristics of the claimed graft simply cannot be expected or predicted from the prior art. Thus, any *prima facie* obviousness, if found to have been properly established, is rebutted.

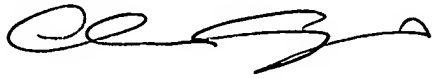
Accordingly, the withdrawal of the §103 rejection based on Bishopric *et al.* or Goldstein *et al.* or Abraham *et al.* in view of Gregory is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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